ORIGINAL RESEARCH

Clinicopathological characteristics and treatment outcomes of adult patients with paratesticular rhabdomyosarcoma (PRMS): A 10-year single-centre experience

Serkan Keskin, MD;* Meltem Ekenel, MD;* Mert Basaran, MD;* Isin Kilicaslan, MD;† Murat Tunc, MD;‡
Sevil Bavbek, MD*

*Department of Medical Oncology, Institute of Oncology, University of Istanbul, Istanbul, Turkey; †Department of Pathology, Istanbul Medical Faculty, University of Istanbul, Istanbul, Turkey; ‡Department of Urology, Istanbul Medical Faculty, University of Istanbul, Istanbul, Turkey.

Abstract

Introduction: We report our experience with 8 consecutive adults treated for paratesticular rhabdomyosarcoma (RMS) at a single institution between 2000 and 2010.
Methods: After primary surgical excision, 7 patients were classified into group I according to the Intergroup Rhabdomyosarcoma Study Group (IRSG) Postsurgical Grouping Classification, and 1 patient into group IIB. Retroperitoneal node dissection was not a required staging procedure. Adjuvant chemotherapy was administered to 7 of the 8 patients. No additional radiotherapy was administered.
Results: The median age at diagnosis was 24 years (range: 18-60). Embryonal histology was the most common (75%) subtype. During follow-up, 3 patients experienced local relapse and 5 distant relapse. The median progression-free and overall survival times were 17.0 ± 9.9 months (range: 5-31) and 27.3 ± 1.3 months (range: 16-58), respectively.
Conclusion: Paratesticular RMS is an uncommon malignancy in adults. We confirm that patients with localized paratesticular RMS may have different prognoses. Retroperitoneal lymphadenectomy can be avoided as a treatment for paratesticular RMS after radical inguinal orchiectomy.

Introduction

Paratesticular rhabdomyosarcoma (RMS) constitutes 7% of all RMS cases in adults.[1] The embryonal subtype is most common when disease is encountered in the paratesticular region.

Paratesticular RMS can develop from mesenchymal elements of the spermatic cord, the epididymis and the testicular envelopes, resulting in development of a pain-free scrotal mass. This superficial location usually facilitates early diagnosis, and complete surgical resection is possible in most patients. However, a substantial proportion of patients with paratesticular neoplasms (26% to 71%) show positive regional lymph nodes.[2] About a third of all patients die from the disease.[3]

The optimal management of paratesticular RMS remains unclear because of the rarity of the disease in adults. Treatment strategies reviewed in the literature include radical inguinal orchiectomy, radiotherapy, retroperitoneal lymph node dissection (RPLND) and chemotherapy. The aim of the present study is to present our experience with patients treated for paratesticular RMS at our centre.

Methods

A sequential and prospectively maintained database at the Institute of Oncology of the University of Istanbul, Turkey, was retrospectively searched for patients who had histologically confirmed paratesticular RMS. Between January 2000 and December 2010, 8 patients fulfilled this criterion, and were included in the present study.

Complete clinical and treatment data were available for all patients. A patient was eligible for inclusion only if his diagnosis had been histologically confirmed. All patients were over 18 years of age.

Staging workup included complete history-taking and a detailed physical examination, complete blood cell and platelet counts, blood chemistry analysis, a testis ultrasound study, and abdominal and chest computed tomography conducted at presentation. Disease staging was performed using the tumour-nodes-metastases (TNM) pretreatment classification[4] and the criteria of the Intergroup Rhabdomyosarcoma Study Group (IRSG) Postsurgical Staging Classification.[5]

All patients underwent surgical resection (radical orchiectomy via inguinal incision with high-level sectioning of the spermatic cord) after histopathological validation after biopsy. Microscopically complete resection with margins

histologically free of cancer was evident in all patients. Surgical assessment of the retroperitoneal lymph nodes was not used as a staging procedure. All patients were restaged in radiographical terms following radical orchiectomy, prior to prescription of adjuvant chemotherapy that commenced within 3 weeks after surgery.

After surgery, seven patients were treated with a combination chemotherapy regimen (VAcdC therapy) composed of vincristine 1.4 mg/m^2 (maximum dose 2 mg) on days 1, 8 and 15; actinomycin D 1.25 mg/m^2 (maximum dose 2 mg) on day 1; and cyclophosphamide 1200 mg/m^2 on day 1, during the 12-month period. Systemic chemotherapy was offered to Patient 3, but the patient refused treatment. Radiotherapy was not used in an adjuvant setting. Objective tumour response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[6]

Follow-up and patient survival

After chemotherapy, patients were followed every 3 months for 2 years, and then at 6 monthly intervals until 5 years had passed. Progression-free survival (PFS) was calculated from the date of surgery to the date of local or distant recurrence. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause, or to the date of the last follow-up. The median follow-up time was calculated as the median observation time for all patients still alive at final follow-up.

This study was approved by the Institutional Review Board of the Institute of Oncology, University of Istanbul, Turkey.

Results

We collected data on the 8 patients (Table 1). Median age at diagnosis was 24 years (range: 18-60). The histologic tumour subtype was embryonal in 6 (75%) patients, alveolar in 1 (12.5%) and pleomorphic in 1 (12.5%). The median tumour diameter was 7.0 ± 1.4 cm (range: 4-9). After primary surgical excision, 7 patients were classified into group I in terms of Intergroup Rhabdomyosarcoma Study Group (IRSG) Postsurgical Grouping Classification, and 1 patient into group IIB. In terms of TNM staging, 6 patients had stage IB disease at presentation, 1 had stage IA, and 1 stage III. The surgical margins were negative for all patients. No solid organ metastasis was detected in any patient at presentation. The median time from symptom onset and presentation at the health care centre was 16.4 ± 26.8 months (range: 10 days-60 months).

Treatment of relapse

During follow-up, local relapse was observed in Patient 3, local relapse and systemic metastasis occurred in Patients 7 and 8, and Patients 5 and 6 showed systemic metastasis only. The most common site of metastasis was the lung, followed by bone.

Patient 3 (with local relapse) was treated via surgery and by application of local radiotherapy (50 Gy), but the patient refused systemic chemotherapy and RPLND. Patient 5 was treated with high-dose melphalan to ensure stem-cell rescue; Patient 6 was retreated with the same VAcdC regimen; whereas Patients 7 and 8 were prescribed adriamycin (75 mg/m^2 on day 1, every 3 weeks) and ifosfamide (2 g/m^2 on days 1-3, every 3 weeks) after relapse. No patient with systemic metastasis responded to such treatment regimens, and best supportive care was offered.

Survival and prognosis

We tallied the disease status (Table 1). The median PFS was 17.0 ± 9.9 months (range: 5-31) and the OS was 27.3 ± 1.3 months (range: 16-58). The prognosis for patients with symptom duration below 1.5 months and/or distant metastasis was poorer than for others (Table 1).

Discussion

In the present study, the median PFS and OS were 17.0 ± 9.9 months (range: 5-31) and 27.3 ± 1.3 months (range: 16-58). The most common histological subtype was embryonal RMS. The PFS and OS of patients with embryonal RMS were longer than in patients with alveolar RMS or paratesticular RMS. No statistically significant association was found between tumour diameter and survival time (data not shown). No significant difference in survival was observed in terms of patient age. An association between symptom duration and survival was evident. Survival of patients with symptom duration less than 1.5 months was poorer compared to that of patients with symptom duration more than 1.5 months. No such outcome was apparent in other studies that included paratesticular RMS patients. A large number of patients must be studied before any generalization is appropriate.

About 70% of genitourinary tract RMS tumours are of the embryonal subtype.[7] In a study by Ferrari and colleagues, the outcomes of 216 patients with paratesticular RMS were reviewed.[8] The histological subtype was embryonal RMS in 181 (84%), alveolar ARMS in 18 (8%), spindle cells in 10 (5%), and "not otherwise specified" in 7 (3%).[8] In our series, 6 patients (75%) were diagnosed with embryonal RMS, whereas our other 2 patients had alveolar RMS and paratesticular RMS (one each).

We prescribed actinomycin D-based chemotherapy in an adjuvant setting for 7 patients. Complete resection of the primary tumour was the treatment of choice in all

Table 1. Patient demographics and disease characteristics

Patient	Age, years	Side	Histol-ogy	Dimen-sions (cm)	IRSG stage	TNM stage	Duration of symptoms*	Adjuvant CT	Local relapse	Meta-stasis	Salvage therapy	Status	PFS (months)	OS (months)
1	24	Left	ERMS	7x9	I	IB	5 years	VAcdC	No	No	–	Healthy	21	21
2	25	Left	ERMS	7x9	I	IB	5 months	VAcdC	No	No	–	Healthy	31	31
3	44	Right	ERMS	4x5	IIB	III	5 years	None	Yes	RPLN	Surgery, RT	AWD	21	31
4	18	Right	ERMS	4x4.5	I	IA	5 months	VAcdC	No	No	–	Healthy	16	16
5	22	Left	ERMS	5x7	I	IB	10 days	VAcdC	No	Lung, bone	HDT/ASCR	Death	6	16
6	23	Left	ERMS	6x7	I	IB	1 month	VAcdC	No	Lung, RPLN	VAdrC	Death	28	58
7	35	Right	ARMS	7x8	I	IB	10 days	VAcdC	Yes	Lung, bone	AI	Death	5	18
8	60	Right	PRMS	5x7	I	IB	1.5 months	VAcdC	Yes	Lung	AI	Death	8	28

ERMS: embryonal rhabdomyosarcoma; TNM: tumour-nodes-metastases; CT: chemotherapy; PFS: progression-free survival; OS: overall survival; VAcdC: vincristine- actinomycin D-cyclophosphamide; RT: radiotherapy; AWD: alive with disease; RPLN, retroperitoneal lymph node; HDT/ASCR; high dose therapy with autologous stem cell rescue; ARMS: alveolar rhabdomyosarcoma; PRMS: pleomorphic rhabdomyosarcoma; IRSG: Intergroup Rhabdomyosarcoma Study Group; AI: adriamycin and ifosfamide. * time between symptom onset and application of therapy.

patients; no patient underwent RPLND. The role of RPLND remains controversial.[9] Some authors recommend the procedure, especially in patients with both paratesticular RMS and high-grade malignant fibrohistiocytoma.[3] Hermans and colleagues described 19 paratesticular RMS patients treated with RPLND, and claimed that a combination of RPLND and systemic chemotherapy afforded a high cure rate.[10] Ferrari and colleagues reported on 44 patients with paratesticular RMS who were generally not given RPLND (the exceptions were patients with enlarged lymph nodes; n = 5); the authors considered that RPLND was unnecessary for localized disease because of the sensitivity afforded by computed tomography, the potential for lymphadenectomy-associated morbidity, the low rate of retroperitoneal recurrence, and the presumed efficacy of chemotherapy in controlling of microscopic disease.[11] An alternative approach toward the treatment of clinically enlarged retroperitoneal lymph nodes involves the use of a more intensive adjuvant chemotherapy regimen. Such an approach is based on results obtained in the IRS-III trial (the Third Intergroup Rhabdomyosarcoma Study), which showed that patients experienced poor outcomes if treated with RPLND followed by chemotherapy with vincristine and dactinomycin. The 5-year survival rates were 69% and 96% in patients with clinically negative nodes treated with and without RPLND, respectively.[12] Chemotherapy can control micrometastases into retroperitoneal nodes when a primary tumour has been completely resected. The main dissemination pattern reflects tumour contiguity with the inguinal canal; cells travelling along this route attain the abdominal cavity. Such findings may explain why neither the prognosis nor survival of patients treated with or without RPLND differ.[13-15] In our present series, no patient was treated with RPLND, although a patient pre-sented with an enlarged lymph node (in the retroperitoneal region) at initial diagnosis. However, no patient experienced recurrence in the retroperitoneal region during follow-up.

The role for adjuvant chemotherapy in adults remains poorly understood.[9,16] Ferrari and colleagues reported that chemotherapy was effective to treat childhood RMS, in an adjuvant setting.[8] Vincristine, dactinomycin, cyclophosphamide, doxorubicin, epidoxorubicin, ifosfamide, carboplatin and etoposide were used in different combinations, and with varying dose schedules, in the cited study. A meta-analysis of genitourinary sarcoma treatments used in 14 randomized trials in various centres showed that doxorubicin-based adjuvant chemotherapy somewhat elongated the time to local and distant failure, but the data were not statistically significant. Also, it was considered that any putative advantage was small, and that such treatment was associated with a considerable degree of toxicity.[17] About a third of patients with paratesticular sarcomas die from metastatic disease.[17,18] In our series, 5 patients (62.5%) developed metastases to retroperitoneal lymph nodes or exhibited systemic dissemination. We believe chemotherapy should be offered as a component of multimodal therapy in patients with paratesticular RMS to control retroperitoneal dissemination and to minimize such dissemination.

The OS rates of patients with pediatric RMS approached 70% with the combined therapy.[19] In a study evaluating RMS at all sites in 2600 patients, adults with RMS experienced significantly worse prognosis than the children (5-year OS rates, $27.0 \pm 1.4\%$ and $61.0 \pm 1.4\%$, respectively; $p < 0.0001$).[20] In another study, in which adult RMS patients also fared more poorly than children, the 5-year adult PFS and OS rates were 28% and 40%, respectively.[21] Survival rate depends, with statistical significance, on tumour histology, diameter, stage

and location, patient age, response to chemotherapy and metastasis status.[8,21-23] Embryonal RMS is a more favourable histological subtype than alveolar or pleomorphic RMS. In our present series, 4 of the 6 patients with ERMS remain alive, but our alveolar RMS and paratesticular RMS patients died during follow-up. Our findings are in line with those of another study.[8]

Associations between symptom duration and length of survival have been evaluated in patients with lung, breast and colorectal cancer. No detailed data, however, are available for patients with sarcomas. In one study, there was no association between symptom duration and length of survival in patients with sarcoma,[23] but another report on patients with osteosarcoma found that symptom and survival duration were linked.[24] However, no prior report has evaluated symptom status and survival duration in paratesticular RMS patients. We suggest that symptom duration is a useful marker when the prognosis of paratesticular RMS patients is to be evaluated.

On the other hand, epididymal inflammation leading to chronic epididymitis can be misdiagnosed as RMS. Although clinical history and the presence of pain help to differentiate epididymal infection from tumour, the diagnosis is not always clear.[25] Mak and colleagues suggested that when encountering an enlarged intrascrotal extratesticular mass with hypervascularity, the following points may be helpful in differentiating RMS from epididymitis: (1) young age and (2) gradual enlargement of testis, not acute onset of symptoms.[26]

Conclusion

Paratesticular RMS may grow rapidly, and must be diagnosed and treated as early as possible. Compared with other studies, we found that the prognosis of adults with paratesticular RMS was poorer than the prognosis of children with paratesticular RMS. Surgical resection is necessary, and combination chemotherapy should be offered to such patients. The embryonal RMS histotype is characteristic of most paratesticular RMS tumours and is associated with optimal prognosis. Alveolar RMS and paratesticular RMS are infrequent conditions; the prognosis of these patients is poorer than the prognosis of patients with embryonal RMS. Survival may depend on the interval between symptom onset and initial presentation.

Competing interests: None declared.

This paper has been peer-reviewed.

References

1. Silvestris N, Zito FA, Resta L, et al. Unique case of giant adult paratesticular spindle cell rhabdomyosarcoma. *Urology* 2009;73:500-2. http://dx.doi.org/10.1016/j.urology.2008.09.025
2. Akbar SA, Sayyed TA, Jafri SZ, et al. Multimodality imaging of paratesticular neoplasms and their rare mimics. *Radiographics* 2003;23:1461-76. http://dx.doi.org/10.1148/rg.236025174
3. Astigueta PJ, Licham MA, Sang PW, et al. Paratesticular sarcoma in adult patients. Disease management and course. *Actas Urol Esp* 2009 33:639-45.
4. Edge SB, Byrd DR, Compton CC, et al. AJCC cancer staging manual (7th ed). 2010;291-8.
5. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. *J Clin Oncol* 2001;19:3091-102.
6. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-16. http://dx.doi.org/10.1093/jnci/92.3.205
7. Dagher R, Helman L. Rhabdomyosarcoma: an overview. *Oncologist* 1999;4:34-44.
8. Ferrari A, Bisogno G, Casanova M, et al. Paratesticular rhabdomyosarcoma: report from the Italian and German Cooperative Group. *J Clin Oncol* 2002;20:449-55. http://dx.doi.org/10.1200/JCO.20.2.449
9. Khoubehi B, Mishra V, Ali M, et al. Adult paratesticular tumours. *BJU Int* 2002;90:707-15. http://dx.doi.org/10.1046/j.1464-410X.2002.02992.x
10. Hermans BP, Foster RS, Bihrle R, et al. Is retroperitoneal lymph node dissection necessary for adult paratesticular rhabdomyosarcoma? *J Urol* 1998;160:2074-7. http://dx.doi.org/10.1016/S0022-5347(01)62246-8
11. Ferrari A, Casanova M, Massimino M, et al. The management of paratesticular rhabdomyosarcoma: a single institutional experience with 44 consecutive children. *J Urol* 1998;159:1031-4. http://dx.doi.org/10.1016/S0022-5347(01)63830-8
12. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol* 1995;13:610-30.
13. Coleman J, Brennan MF, Alektiar K, et al. Adult spermatic cord sarcomas: management and results. *Ann Surg Oncol* 2003;10:669-75. http://dx.doi.org/10.1245/ASO.2003.11.014
14. Ballo MT, Zagars GK, Pisters PW, et al. Spermatic cord sarcoma: outcome, patterns of failure and management. *J Urol* 2001;166:1306-10. http://dx.doi.org/10.1016/S0022-5347(05)65758-8
15. Catton C, Jewett M, O'Sullivan B, et al. Paratesticular sarcoma: failure patterns after definitive local therapy. *J Urol* 1999;161:1844-7. http://dx.doi.org/10.1016/S0022-5347(05)68823-4
16. Ferrari A, Casanova M. Current chemotherapeutic strategies for rhabdomyosarcoma. *Expert Rev Anticancer Ther* 2005;5:283-94. http://dx.doi.org/10.1586/14737140.5.2.283
17. Mondaini N, Palli D, Saieva C, et al. Clinical characteristics and overall survival in genitourinary sarcomas treated with curative intent: a multicenter study. *Eur Urol* 2005;47:468-73. http://dx.doi.org/10.1016/j.eururo.2004.09.013
18. Dotan ZA, Tal R, Golijanin D, et al. Adult genitourinary sarcoma: the 25-year Memorial Sloan-Kettering experience. *J Urol* 2006;176:2033-8; discussion 8-9. http://dx.doi.org/10.1016/j.juro.2006.07.021
19. Hawkins WG, Hoos A, Antonescu CR, et al. Clinicopathologic analysis of patients with adult rhabdomyosarcoma. *Cancer* 2001;91:794-803. http://dx.doi.org/10.1002/1097-0142(20010215)91:4<794::AID-CNCR1066>3.0.CO;2-Q
20. Sultan I, Qaddoumi I, Yaser S, et al. Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: an analysis of 2,600 patients. *J Clin Oncol* 2009;27:3391-7. http://dx.doi.org/ 10.1200/JCO.2008.19.7483
21. Ferrari A, Dileo P, Casanova M, et al. Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution. *Cancer* 2003;98:571-80. http://dx.doi.org/10.1002/cncr.11550
22. Kosan M, Gonulalan U, Ugurlu O, et al. Embryonal paratesticular rhabdomyosarcoma: a case of young adult patient who has inguinal relapse. *Int Urol Nephrol* 2007;39:1159-61. http://dx.doi.org/10.1007/s11255-006-9070-0
23. Esnaola NF, Rubin BP, Baldini EH, et al. Response to chemotherapy and predictors of survival in adult rhabdomyosarcoma. *Ann Surg* 2001;234:215-23. http://dx.doi.org/10.1097/00000658-200108000-00012
24. Rougraff BT, Davis K, Lawrence J. Does length of symptoms before diagnosis of sarcoma affect patient survival? *Clin Orthop Relat Res* 2007;462:181-9. http://dx.doi.org/10.1097/BLO.0b013e3180f62608
25. Sung T, Riedlinger WF, Diamond DA, et al. Solid extratesticular masses in children: radiographic and pathologic correlation. *AJR Am J Roentgenol* 2006;186:483-90. http://dx.doi.org/10.2214/AJR.04.1895
26. Mak CW, Chou CK, Su CC, et al. Ultrasound diagnosis of paratesticular rhabdomyosarcoma. *Br J Radiol* 2004;77:250-2. http://dx.doi.org/10.1259/bjr/20564274

Correspondence: Dr. Serkan Keskin, Istanbul Universitesi Onkoloji Enstitusu, Capa - 34093 Istanbul, Turkey; fax: + 90 212 534 80 78; drkeskin76@hotmail.com